EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Administration of hepatitis B vaccine in winter as a significant predictor of the poor effectiveness of vaccination in rural Mongolia: evidence from a nationwide survey

Dambadarjaa Davaalkham, Toshiyuki Ojima, Steven Wiersma, Tserenkhuu Lkhagvasuren, Pagvajav Nymadawa, Ritei Uehara, Makoto Watanabe, Izumi Oki, Yosikazu Nakamura

J Epidemiol Community Health 2007;**61**:578–584. doi: 10.1136/jech.2006.051375

See end of article for authors' affiliations

Correspondence to:
Dr D Davaalkham, Department of Public Health, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan; davaamon@jichi.ac.jp

Accepted 13 October 2006

Background: Universal hepatitis B (HB) immunisation is the most effective means for prevention of hepatitis B virus (HBV) infection worldwide. Maintaining the vaccine cold chain is an essential part of a successful immunisation programme. Our recent nationwide survey in Mongolia has observed significant urban–rural differences in the prevalence of HBV infection among vaccinated cohorts.
Objective: To examine whether the administration of HB vaccine in winter contributes to these residential discrepancies on the effectiveness of vaccination.
Design and setting: In 2004, a nationwide serosurvey was carried out covering both urban and rural areas of Mongolia. Sampling was multistage, with random probability from all public schools in the country.
Participants: A random sample of 1145 children (51.7% boys; aged 7–12 years), representative of Mongolian elementary school children.
Results: Multivariate logistic regression analysis identified that total (past and current) HBV infection (OR 2.31, 95% CI 1.20 to 4.42; p = 0.012) was independently associated with the administration of all HB vaccines in winter. An increased OR for current HBV infection was also observed (OR 2.58, 95% CI 0.87 to 7.68; p = 0.089), but without significance. Interestingly, after stratifying by residence, the association between winter vaccination and total HBV infection was evident for rural (p = 0.008) but not for urban areas (p = 0.294). The frequency of vaccine-induced immunity was significantly (p = 0.007) lower for those who received HB vaccine at birth during winter in rural areas.
Conclusion: Administration of HB vaccine during winter is an important predictor of the low effectiveness of vaccination in rural Mongolia. To improve the effectiveness of HB vaccination in remote areas, cold chain control should be addressed with particular attention to the winter season.

The development and availability of highly effective vaccines against hepatitis B (HB) since 1982 represent a major advancement in preventive medicine and public health.[1] In accordance with recommendations made by the World Health Organization (WHO) in 1992, more than 150 countries now offer HB vaccine to all children,[2] with subsequent dramatic decreases in the incidence of hepatitis B virus (HBV) infection among infants, children and adolescents.[3]

Maintaining the vaccine cold chain is an essential part of a successful immunisation programme because vaccines lose their immunological potency on exposure to extreme temperatures.[4] The availability of vaccine vial monitors to guarantee that vaccine potency had not been compromised by excessive exposure to heat has been an important global strategy to prevent damage due to heat. Despite dramatic improvements in protection from heat damage, however, damage due to freezing remains a significant under-recognised and under-reported cause of vaccine wastage and lost potency, especially for expensive and freeze-sensitive vaccines such as the HB vaccine.[5] The WHO's guidelines on the introduction of HB vaccine recommend that it should be stored at 2–8℃ and must not be frozen, because the reported freezing point of HB vaccine is −0.5℃ and a single freeze of HBV vaccine will virtually eliminate its immunogenicity.[6 7]

Inadequate cold chain control or improper storage of vaccines of the Expanded Program on Immunization (EPI) has been reported in both developed and developing countries of the world, including the UK,[4 8] Italy,[9] Australia,[10 11] Hungary,[12] Malaysia[13] and the US.[14] An inadvertent freezing of HB vaccine due to the inappropriate storage and handling has also been reported from Indonesia,[5] Malaysia[13] and Mongolia.[15] However, the environmental effect, or in particular the impact of a cold winter season on the freezing of HB vaccine, has not been studied either in Mongolia or in the world so far.

Located in central Asia at an altitude of 1500 metres above sea level, Mongolia has an extreme continental climate with long, cold winters and short summers. The average temperatures in January (the coldest period) range between −15℃ in the south and −32℃ in the north, and the sub zero temperatures continue from November through April.[16] It has been previously estimated that HBV infection is highly prevalent in Mongolia.[17–19] The mass infant HB vaccination was initiated in 1991, aiming to decrease the incidence of HBV infection and its serious consequences, including cirrhosis and hepatocellular carcinoma. Our recent nationwide survey[20] of the generation born after the start of this programme showed meaningful declines in the prevalence of total (15.8%) and current (5.2%) HBV infections in Mongolia, which have mainly been achieved through the mass HB vaccination. Nevertheless, significant differences in the prevalence of both current (3.0% vs 7.7%, $p<0.001$) and total HBV infections (11.2% vs 21.0%, $p<0.001$) among vaccinated cohorts have been observed between urban and rural areas. We hypothesise that these

Abbreviations: anti-HBc, antibody against hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; EPI, Expanded Program on Immunization; HB, hepatitis B; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; WHO, World Health Organization high rates of HBV infection observed among rural vaccinated cohorts could have been attributed to freezing of HB vaccine during the cold winter months. In this paper, we present data from a nationwide survey examining the association between administration of HB vaccines during the winter season and the residential discrepancies on the effectiveness of HB vaccination.

METHODS

Study design and participants

We conducted a nationwide school-based cross-sectional serosurvey of vaccinated cohorts throughout Mongolia. The study design and sampling method have been described in detail elsewhere.[20 21] In brief, the sampling of the study population was carried out with a stratified, multistage, random cluster method from all public schools (n = 593) in the country. Schools and second grade elementary classrooms were selected with probability proportional to the size of the corresponding population to ensure the self-weighting of the sample. All children in the selected classrooms were eligible for the study.

The field work for this survey was conducted between October and November 2004. The HB vaccination history was extracted from immunisation cards or registries at local health centres and family hospitals. Information regarding the student's sociodemographic characteristics, including date of birth, sex, place of residence, ethnicity, parents' occupation, type of dwelling and family size, as well as information on potential risk factors of HBV infection were recorded from school registers or through interview with parents.

Laboratory analysis

Serum specimens of all study subjects were analysed for hepatitis B surface antigen (HBsAg), the corresponding antibody to HBsAg (anti-HBs), and the antibody against hepatitis B core antigen (anti-HBc) using commercially available chemiluminescence immunoassay kits (Abbott Japan, Tokyo, Japan).

Assessment of HB vaccination coverage of study subjects

Since its introduction into the national EPI programme, different brands of HB vaccine have been used in Mongolia with principal funding from the Mongolian government and international agencies. The children in this survey were vaccinated with plasma-derived vaccines of High Immunogenic Hepatitis B Vaccine (HIHBV, Democratic People's Republic of Korea) at birth and at 2 months, or Hepaccine B (Cheil Foods and Chemicals Company, Seoul, Republic of Korea) at birth, 2 months and 8 months. For every child who had immunisation documentation, the administration regimen of HB vaccine was determined and coverage of complete vaccination was

Table 1 Characteristics of study sample by residence

Characteristics	Total* (n = 1145)	Urban (n = 626)	Rural (n = 519)	p Value
Mean (SD) age	8.5 (0.8)	8.6 (0.8)	8.5 (0.8)	0.001
Sex, n (%)				0.526
Boys	592	329 (52.6)	263 (50.7)	
Girls	553	297 (47.7)	256 (49.3)	
Ethnicity, n (%)				<0.001
Khalkh (majority)	1007	599 (95.7)	408 (78.6)	
Non-Khalkh (minority)	138	27 (4.3)	111 (21.4)	
Housing, n (%)				<0.001
Apartment	178	171 (27.9)	7 (1.5)	
Ger	537	258 (42.0)	279 (58.7)	
Others	374	185 (30.1)	189 (39.8)	
Family size, n (%)				<0.001
<4 members	538	192 (40.4)	346 (56.4)	
⩾5 members	551	283 (59.6)	268 (43.6)	
Father's occupation, n (%)				<0.001
Professionals	173	136 (21.7)	37 (7.1)	
Herdsman	204	26 (4.2)	178 (34.3)	
Others	768	464 (74.1)	304 (58.6)	
Mother's occupation, n (%)				<0.001
Professionals	364	269 (43.0)	95 (18.3)	
Herdsman	221	27 (4.3)	194 (37.4)	
Others	560	330 (52.7)	230 (44.3)	
HBV-infected mother				0.194
Yes	81	38 (7.3)	43 (9.6)	
No	891	485 (92.7)	406 (90.4)	
Birth HB dose†, n (%)				0.741
Winter administration	345	115 (50.0)	230 (51.3)	
Non-winter administration	333	115 (50.0)	218 (48.7)	
Total HB doses†, n (%)				0.032
All administered in winter	180	65 (26.9)	115 (25.5)	
Some administered in winter	326	99 (40.9)	227 (50.3)	
None administered in winter	187	78 (32.2)	109 (24.2)	

HB, hepatitis B; HBV, hepatitis B virus.
*Total number in some variables may not equal 1145, due to missing values and unknown answers.
†Analysed for those who have immunisation documentation (n = 702).

assessed by measuring the validity of HB doses as follows. A dose given within 48 h of birth (or within 2 days in this study) was considered as a valid HB-birth dose; valid second HB (HB2) was considered as a dose delivered at least 4 weeks after HB-birth dose and before the first birthday; and valid third (HB3) dose (if administered) was considered as a shot that was given at least 4 weeks after HB2 and before the first birthday. According to the above criteria, vaccination status for HB was defined as complete (those who received all HB vaccine shots within the schedule), incomplete and none.

Definitions

Immunity due to vaccination was considered as the presence of anti-HBs alone, with a titre of $\geqslant$10 mIU/ml. Serological evidence of past HBV infection was defined as anti-HBc positivity. Current infection was defined as positive for HBsAg, and the total HBV infection included both past and current infections (HBsAg and/or anti-HBc positive).

The long, cold winter season with temperature below freezing in the country meant that the months between November and April were considered as ''winter'' in the analyses.

In this study, Metropolitan cities and central towns of the provinces were defined as ''urban'', and rural villages (Soum in Mongolian) were defined as ''rural'' areas.

Statistical methods

The magnitude of association between administration of birth or all HB doses and HBV infection as well as immunity induced by vaccination were summarised as an odds ratio (OR) with 95% CI. Multivariate logistic regression models were used to assess independent predictors of differences in the HBV infection and immunity level between urban and rural areas. The χ^2 test or Fisher's exact tests have also been used where appropriate. Two-sided significance tests are reported. In the analyses, sampling weight was not incorporated because of the equal probabilities of sample selection. The analyses were performed in SPSS V.12.01.

The study was approved by the ethical review committees of the WHO; Ministry of Health, Mongolia; and Jichi Medical University, Japan.

RESULTS

Among 1271 children in the randomly selected classrooms, 1182 (93%) children agreed to participate, and the blood samples were available for 1145 children. Table 1 shows the characteristics of the study sample in terms of sociodemographic variables, mother's status of HBV infection and winter administration of HB vaccines by urban–rural residence. The age of the study population ranged from 7 to 12 years (mean (SD) 8.5 (0.7) years); 54.7% were from urban areas. As was expected, non-Khalkh or minority ethnic group children (21.4% vs 4.3%, $p<0.001$) and those from a herdsman family (herdsman father 34.3% vs 4.2%, $p<0.001$, herdsman mother 37.4% vs 4.3%, $p<0.001$) living in Ger dwelling, a Mongolian style lodging (58.7% vs 42.0%, $p<0.001$), were more common in rural areas compared with urban areas. There were no significant differences, however, in the distributions of sex, HBV-infected mother and winter administration of birth HB vaccines between urban and rural areas.

Analysis of the associations of sociodemographic variables, exposures to health risks and family history with the status of HBV infection and vaccine-induced immunity is shown in table 2. Age, male sex, rural residence, having herdsman parents and living in Ger dwelling were significantly associated with both current and total HBV infections among the study subjects. Children who have HBV-infected mothers were significantly more likely to have current HBV infection than those having mothers without HBV infection.

Further logistic regression analyses on the association of winter vaccination with HBV infection and vaccine-induced immunity were carried out for those who had immunisation documentations (n = 702, 61.3%), from where the HB vaccination histories were abstracted. Mother's information about HB vaccination of her child was not used in the analyses owing to the potential recall bias and inaccuracy. In univariate analyses, total HBV infection was significantly associated with administration of some (OR = 2.04, 95% CI 1.19 to 3.49, p = 0.009) or all doses (OR = 2.31, 95% CI 1.29 to 4.14, p = 0.005) of HB vaccine during the winter months. The corresponding ORs of current HBV infection for vaccinees receiving some and all doses of HB vaccine in winter were 2.18 (95% CI 0.87 to 5.49; p = 0.097) and 2.54 (95% CI 0.96 to 6.77; p = 0.062), respectively, compared with those vaccinated during non-winter months (table 3). Total HBV infection (OR = 1.63, 95% CI 1.09 to 2.44, p = 0.016) was also significantly associated with winter administration of birth HB vaccine. In the multivariate regression model that adjusted for confounding variables of age, sex, residence, ethnicity, family size, housing type, maternal and paternal occupation, mother's status of HBV infection and completeness of HB vaccination, the above results were not substantially attenuated: those who received all HB vaccines in winter had 2.31-fold significantly (p = 0.012) increased risk of being infected with HBV and 2.58 fold increased risk of having current HBV infection, although the latter could not reach significance (p = 0.089) compared with those who were vaccinated during non-winter months. In contrast, a slightly decreased OR without significance for vaccine-induced immunity was observed in univariate analysis (OR = 0.69, 95% CI 0.45 to 1.04, p = 0.075) on winter birth HB vaccination, which has also remained low (OR = 0.66, 95% CI 0.42 to 1.05, p = 0.078) after adjustment for the above potential confounding variables.

Of note is that, after stratifying by residence, these associations were more evident for rural subjects but not for urban children (table 4). The prevalence of total HBV infection was significantly higher among rural subjects receiving birth HB in winter than those vaccinated during non-winter months (25.7% vs 17.0%, p = 0.025), which was likely to increase with the number of vaccines given in winter (p = 0.008). A similar increasing trend was observed for current HBV infection, but without significance (p = 0.138). Interestingly, in rural areas, the frequency of immunity induced by vaccine was significantly lower among those with winter administration of birth HB than those vaccinated during non-winter months (p = 0.007). However, this difference was not evident in urban areas.

DISCUSSION

Careful attention to storage and handling is essential to ensure optimal potency of vaccines and to maximise the resulting efficacy of immunisation.[14] However, the cold chain still remains a highly vulnerable element of any immunisation programme, both in developing and developed countries.[9] To the best of our knowledge, this is the first paper to evaluate the impact of winter season on HB vaccine-freezing. Our findings have important implications for further research on public health measures aimed at improving the effectiveness of vaccination in the remote areas of Mongolia as well as in other countries where applicable.

In the present study, we observed an independent association of winter administration of HB vaccine with total HBV infection, in both univariate and multivariate regression analyses. In addition, although we could not reach statistical significance mainly due to the limited number of subjects in

Table 2 Univariate logistic regression analyses for the association of hepatitis B virus infection and vaccine-induced immunity with sociodemographic variables, exposure to health risks and family history: OR and 95% CI

Variables	Current HBV infection	Total HBV infection	Vaccine-induced immunity
Sociodemographic variables			
Age† (1-year increase)	1.58 (1.17 to 2.15)**	1.55 (1.27 to 1.89)***	0.87 (0.71 to 1.07)
Sex			
Girls	1 (reference)	1 (reference)	1 (reference)
Boys	1.88 (1.08 to 3.26)*	1.43 (1.04 to 1.97)*	1.20 (0.88 to 1.63)
Residence			
Urban	1 (reference)	1 (reference)	1 (reference)
Rural	2.67 (1.53 to 4.67)***	2.10 (1.52 to 2.91)***	0.81 (0.59 to 1.11)
Ethnicity			
Khalkh	1 (reference)	1 (reference)	1 (reference)
Non-Khalkh	1.34 (0.64 to 2.78)	1.50 (0.96 to 2.33)	0.97 (0.60 to 1.56)
Father's occupation			
Professionals	1 (reference)	1 (reference)	1 (reference)
Herdsman	4.34 (1.45 to 13.01)**	2.77 (1.57 to 4.91)***	0.60 (0.34 to 1.04)
Others	2.08 (0.73 to 5.92)	1.36 (0.81 to 2.27)	0.87 (0.57 to 1.33)
Mother's occupation			
Professionals	1 (reference)	1 (reference)	1 (reference)
Herdsman	3.93 (1.75 to 8.78)**	2.88 (1.85 to 4.50)***	0.62 (0.39 to 1.0)
Others	2.23 (1.05 to 4.76)*	1.41 (0.94 to 2.11)	0.91 (0.65 to 1.28)
Housing type			
Apartment	1 (reference)	1 (reference)	1 (reference)
Ger	3.22 (1.13 to 9.16)*	2.17 (1.26 to 3.74)**	0.67 (0.44 to 1.02)
Others	1.69 (0.55 to 5.22)	1.60 (0.90 to 2.85)	0.68 (0.43 to 1.07)
Number of household members			
<4	1 (reference)	1 (reference)	1 (reference)
$\geqslant 5$	1.38 (0.80 to 2.39)	1.46 (1.05 to 2.03)*	0.90 (0.65 to 1.23)
Exposure to health risks‡			
Hospitalisation	1.00 (0.58 to 1.73)	0.89 (0.64 to 1.24)	1.20 (0.87 to 1.66)
Surgery	1.06 (1.04 to 1.07)	0.84 (0.35 to 2.02)	0.77 (0.32 to 1.86)
Acupuncture	1.28 (0.17 to 9.94)	1.96 (0.62 to 6.24)	1.84 (0.58 to 5.85)
Blood test	1.16 (0.63 to 2.15)	0.96 (0.65 to 1.42)	1.19 (0.82 to 1.73)
Injection at the hospital	1.18 (0.67 to 2.07)	0.99 (0.70 to 1.39)	1.04 (0.74 to 1.46)
Family history‡			
HBV-infected mother	3.43 (1.68 to 7.0)**	1.53 (0.87 to 2.69)	1.10 (0.61 to 1.97)
Cohabitating with patient with chronic HB	2.56 (1.35 to 4.88)**	1.52 (0.96 to 2.40)	1.05 (0.64 to 1.72)
Cohabitating with patient with liver cancer	1.60 (0.37 to 6.97)	1.41 (0.52 to 3.82)	0.95 (0.32 to 2.82)
Cohabitating with patient with liver cirrhosis	1.72 (0.51 to 5.82)	1.12 (0.46 to 2.74)	1.22 (0.52 to 2.82)

HB, hepatitis B; HBV, hepatitis B virus.
*$p<0.05$.
**$p<0.01$.
***$p<0.001$.
†Age range of study population is 7–12 years.
‡Reference variables do not have history of exposure to health risks and family history of HBV.

that category, current HBV infection also had an increased OR of more than twofold for winter HB vaccination even in adjusted models for potential confounders. Interestingly, winter administration of the birth HB dose was associated with decreased immunity level induced by vaccination in rural areas, suggesting a negative effect of the winter season on effectiveness of the vaccine.

HB vaccines are highly immunogenic, even in preterm-newborns, and can induce protective anti-HBs in >95% of infants. Several factors that have been reported to be associated with non-response to HB vaccine, including male sex, advancing age (⩾40 years), obesity, smoking, chronic illness and immunosuppression,[1] might not be applicable for infants. In addition, it has been suggested that a vaccine-induced mutant of HBsAg could be one of the potential causes for the failure of response to HB vaccine.[22] However, we did not find any of the well-known vaccine-escape mutations in the S gene of HBV, such as G145R, among the HBV-infected subjects of this study, suggesting that the S gene mutant is not a potential cause for vaccine failure in Mongolia.[23]

According to the HB vaccination coverage in urban and rural areas, there were no significant differences in the coverage of timely—given birth-HB vaccine (67.6% vs 63.1%, $p = 0.230$) and complete HB vaccination (61.9% vs 59.1%, $p = 0.466$) between urban and rural areas. However, it should be noted that the HB coverage of birth (59.8% vs 75.2%, $p = 0.010$) and complete HB vaccination (55.7% vs 68%, $p = 0.047$) were significantly different within the urban areas or between province centres and metropolitan areas.[24] In the present study, to better estimate the impact of winter season on effectiveness of HB vaccination in the country, we included the completeness of HB vaccination in multivariate regression models. Therefore,

Table 3 Relationships of hepatitis B virus infection and vaccine-induced immunity with winter administration of hepatitis B vaccine

Variables	Current HBV infection		Total HBV infection		Vaccine-induced immunity	
	Crude OR (95% CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Winter administration of birth HB Vaccine						
No	1	1	1	1	1	1
Yes	1.25 (0.66 to 2.36)	1.36 (0.67 to 2.78)	1.63 (1.09 to 2.44)*	1.71 (1.08 to 2.70)*	0.69 (0.45 to 1.04)	0.66 (0.42 to 1.05)
Winter administration of total HB raccine						
None	1	1	1	1	1	1
Some doses	2.18 (0.87 to 5.49)	2.12 (0.76 to 5.89)	2.04 (1.19 to 3.49)**	1.75 (0.96 to 3.20)	1.20 (0.74 to 1.96)	1.21 (0.71 to 2.08)
All doses	2.54 (0.96 to 6.77)	2.58 (0.87 to 7.68)	2.31 (1.29 to 4.14)**	2.31 (1.20 to 4.42)*	0.68 (0.37 to 1.25)	0.62 (0.31 to 1.23)

HB, hepatits B; HBV, hepatitis B virus.
*$p<0.05$.
**$p<0.01$.
†Adjusted for age, sex, residence, ethnicity, family size, housing type, maternal and paternal occupation, mother's status of HBV infection and completeness of vaccination.

we assume that the results of this study show an independent association of winter vaccination with HBV infection and vaccine-induced immunity.

In endemic areas of HBV infection where >8% of the general population are chronic carriers of HBV, the most common route of transmission is perinatal or from a carrier mother to a neonate, and virus persists after infection in as many as 90% of infants infected perinatally.[25] Consistently, children who reported to have a mother infected with HBV were significantly more likely to have current HBV infection than those who did not. Moreover, in the risk factor analysis, no association was found between HBV infection and parenteral exposures to potential risks at the healthcare settings, suggesting that HBV was more efficiently transmitted by vertical route or from the infected mother in Mongolia.

The current national immunisation schedule is mandatory for all Mongolian citizens of eligible age, and EPI vaccinations are carried out in state-owned health facilities at no cost. All HB vaccine is imported to the national store located in capital city of Ulaanbaatar, Mongolia. Vaccines from every shipment are distributed evenly across the country. In the city of Ulaanbaatar itself, local health centres collect their vaccines directly from the national store every month, and store them in refrigerators of health centres. Vaccines are distributed by a two-stage procedure in rural areas. Every 3 months, vaccines are distributed from the national store to provincial stores by train or airplane. Then the vaccines are monthly transported to rural Soum health centres, which use refrigerators for storage. Travel times vary with proximity of the Soum to the province centre (range: 5–380 km, average 140 km), time of year, weather and vehicle reliability, varying from as short as 1-h round-trip to as long as 10 h in each direction.[15 26] Sparse population (only 1.5 inhabitants per square kilometre) and difficult terrain with harsh climate make the delivery of vaccines more difficult.

A recent cold chain study by Edstam *et al*[15] has observed an exposure of HB vaccine to freezing temperatures during the transport from Province centres to rural health centres in Mongolia. The authors speculated that vaccines transported with ice packs taken directly from deep freezes at −20℃ was the cause of freezing.[15] We assume that the harsh winter season of Mongolia might have also played a role in the freezing of HB vaccines during transport and storage in the remote areas.

Table 4 Frequencies of hepatitis B virus infection and vaccine-induced immunity according to winter administration of hepatitis B vaccine stratified by residence

	Winter administration of birth HB			Winter administration of total HB			
	No	Yes	p Value*	None	Some	All doses	Trend p†
Total HBV infection, n (%)							
Urban	10 (8.7)	14 (12.2)	0.388	4 (5.1)	6 (16.2)	6 (9.2)	0.294
Rural	37 (17.0)	59 (25.7)	0.025	16 (14.7)	48 (21.1)	33 (28.7)	0.008
Total	47 (14.7)	73 (21.2)	0.016	20 (10.7)	64 (19.6)	39 (21.7)	0.005
Current HBV infection, n (%)							
Urban	2 (1.7)	3 (2.6)	0.685	0	4 (4.0)	2 (3.1)	0.129
Rural	16 (7.3)	20 (8.7)	0.598	6 (5.5)	18 (7.9)	12 (10.4)	0.138
Total	18 (5.4)	23 (6.7)	0.491	6 (3.2)	22 (6.7)	14 (7.8)	0.051
Vaccine-induced immunity, n (%)							
Urban	16 (13.9)	20 (17.4)	0.468	10 (12.8)	16 (16.2)	11 (16.9)	0.418
Rural	45 (20.6)	26 (11.3)	0.007	19 (17.4)	43 (18.9)	9 (7.8)	0.056
Total	61 (18.3)	46 (13.3)	0.075	29 (15.5)	59 (18.1)	20 (11.1)	0.288

HB, hepatitis B; HBV, hepatitis B virus.
*Calculated using the χ^2 test or Fisher's exact test.
†Calculated using the extended Mantel–Haenszel χ^2 test for trend.

Studies on the cold chain control and management of vaccine handling and transportation in other countries have demonstrated the poor knowledge and practice in the appropriate management of vaccine storage and handling; failure to monitor temperatures in the freezer or refrigerator, and in all cold storage compartments was the main reason for improper vaccine handling.[12 27 28] In addition, limited knowledge and skills in the proper use of equipment, low technical capacity for repairs and maintenance of equipment, particularly at the lower levels, inadequate infrastructure in rural areas, specifically a chronic lack of and/or irregular electricity supply, could be making the cold chain vulnerable in Mongolia.[26]

In many developing countries in Asia, birth dose is currently unavailable because of the difficulty of keeping vials at the manufacturer's recommended temperature. To achieve better coverage of birth HB vaccine, several semi-tropical countries including Indonesia[29] and Vietnam[30] have carried out pilot projects to store and deliver HB outside of the cold chain, based on known heat stability of the HBsAg and availability of vaccine vial monitors to monitor vaccine storage conditions.[31] However, such a project would not be appropriate in Mongolia, due to the difficulties in protecting the freeze-sensitive HB vaccine from freezing temperature during the long, cold winter season of the country. In addition, this project is efficient for countries with high rate of home birth such as Vietnam (average home birth rate 23.1%), to increase the coverage of birth HB dose, delivering the vaccine in their homes.[30] Mongolia has a high coverage of vaccination, reaching 98.2% for HB vaccination and 97.7–99% for other EPI vaccines by 2004. According to the statistical report of the Ministry of Health, home delivery rate is low in Mongolia, accounting for only 0.8% of all deliveries in 2004.[32]

The limitations of this study may include that the association of winter HB vaccination with HBV infection and vaccine-induced immunity was evaluated for those (n = 702) who had immunisation documentations, from which the HB vaccination history was recorded. This could have led to the small number of children in some categories such as those with current HBV infection, resulting in the lack of statistical significance of the outcome. However, the analysis on the associations of socio-demographic characteristics, health-related risks and family history with HBV infection and immunity were performed for all study subjects (n = 1145).

Despite the above limitation, the observation of the potential impact of winter season on the effectiveness of universal HB vaccination using a geographically representative random sample of the young generation born after the start of the vaccination programme in Mongolia, which is the first that has been reported in the world so far, can be considered as a strength of this study.

What is already known on the topic

- Universal infant immunisation with hepatitis B vaccine is the most effective means for prevention of hepatitis B virus infection and its serious complications, including hepatocellular carcinoma, worldwide.
- However, the potency of vaccines depends on protecting them from damage due to freezing and heat.
- Despite dramatic improvements in protection from heat damage, freeze damage remains a significant under-recognised and under-reported cause of vaccine wastage and lost potency worldwide.

What this paper adds

- This paper first reports the impact of winter season on the effectiveness of hepatitis B (HB) vaccination worldwide.
- Our results, using nationwide survey data, suggest that the poor effectiveness of mass HB vaccination in rural areas could be attributed to freezing of HB vaccine during the cold winter months in Mongolia.

Policy implications

- The findings of this study have important implications for further research and public health measures aimed at improving the effectiveness of vaccination in the remote areas of Mongolia, as well as in other countries where applicable.
- There is an urgent need to improve the monitoring and control of vaccine cold chain in rural areas, with particular attention to winter season in order to prevent the damage of hepatitis B vaccine and to improve effectiveness of infant vaccination.
- The training of vaccine staff in proper management of vaccine storage and handling is important.
- The use of cold chain monitors, particularly those for cold temperatures, would be useful to monitor cold chain accurately and efficiently.

The findings of this study demonstrate that the administration of HB during winter season might have played an important role in the high prevalence of HBV infection and low rate of vaccine-induced immunity in rural areas of Mongolia. To increase the vaccination effectiveness in remote areas, maintenance of cold chain during transportation and storage should be addressed with particular attention to cold winter season. The training of vaccine staff in proper management of vaccine storage and handling is important, and the use of cold-chain monitors, particularly those for cold temperatures, would be useful to monitor cold chain accurately and efficiently.

ACKNOWLEDGEMENTS

We thank the health personnel and school teachers in each study area, as well as our participants, without whose efforts the project could not have been completed.

....

Authors' affiliations

Dambadarjaa Davaalkham, Toshiyuki Ojima, Ritei Uehara, Makoto Watanabe, Izumi Oki, Yosikazu Nakamura, Department of Public Health, Jichi Medical University School of Medicine, Tochigi, Japan
Steven Wiersma, Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
Tserenkhuu Lkhagvasuren, Health Sciences University, Ulaanbaatar, Mongolia
Pagvajav Nymadawa, National Center for Communicable Diseases, Ulaanbaatar, Mongolia

Funding: This study was supported by grants from the World Health Organization, Switzerland (Number WP/MOG/IVD/216/XC/04991.00) and Jichi Medical University, Japan.

Competing interests: None.

This study was approved by the Ethical Review Committees of the World Health Organization, Switzerland; Ministry of Health, Mongolia; and Jichi Medical University, Japan.

REFERENCES

1 **Zuckerman JN**. Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines. *J Med Virol* 2006;**78**:169–77.
2 **World Health Organization**. *WHO vaccine-preventable diseases: monitoring system, 2004 global summary*. Geneva: WHO, 2004.
3 **Lavanchy D**. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004;**11**:97–107.
4 **Cheriyan E**. Monitoring the vaccine cold chain. *Arch Dis Child* 1993;**69**:600–1.
5 **Nelson CM**, Wibisono H, Purwanto H, *et al*. Hepatitis B vaccine freezing in the Indonesian cold chain: evidence and solutions. *Bull World Health Organ* 2004;**82**:99–105.
6 **Galazka A**, Milstein J, Zaffran M. *Thermostability of vaccine*, WHO document WHO/GPV/98.07. Geneva: World Health Organization, 1998.
7 **Diminsky D**, Moav N, Gorecki M, *et al*. Physical, chemical and immunological stability of CHO-derived hepatitis B surface antigen (HBsAg) particles. *Vaccine* 1999;**18**:3–17.
8 **Haworth EA**, Booy R, Stirzaker L, *et al*. Is the cold chain for vaccines maintained in general practice? *BMJ* 1993;**307**:242–4.
9 **Grasso M**, Ripabelli G, Sammarco ML, *et al*. Vaccine storage in the community: a study in central Italy. *Bull World Health Organ* 1999;**77**:352–5.
10 **Jeremijenko A**, Kelly H, Sibthorpe B, *et al*. Improving vaccine storage in general practice refrigerators. *BMJ* 1996;**312**:1651–2.
11 **Guthridge SL**, Miller NC. Cold chain in a hot climate. *Aust N Z J Public Health* 1996;**20**:657–60.
12 **Lugosi L**, Battersby A. Transport and storage of vaccines in Hungary: the first cold chain monitor study in Europe. *Bull World Health Organ* 1990;**68**:431–9.
13 **Hanjeet K**, Lye MS, Sinniah M, *et al*. Evaluation of cold chain monitoring in Kelantan, Malaysia. *Bull World Health Organ* 1996;**74**:391–7.
14 **Bishai DM**, Bhatt S, Miller LT, *et al*. Vaccine storage practices in pediatric offices. *Pediatrics* 1992;**89**:193–6.
15 **Edstam JS**, Nyamkhuu D, Orgil T, *et al*. Exposure of hepatitis B vaccine to freezing temperatures during transport to rural health centers in Mongolia. *Prev Med* 2004;**39**:384–8.
16 **Ministry of Health, Government of Mongolia**. *Health Sector Review-Mongolia*. Ulaanbaatar: Ministry of Health, Government of Mongolia, 1999.
17 **Goldstein ST**, Zhou F, Hadler SC, *et al*. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *Int J Epidemiol* 2005;**34**:1329–39.
18 **Fujioka S**, Shimomura H, Ishii Y, *et al*. Prevalence of hepatitis B and C virus markers in outpatients of Mongolian general hospitals. *Kansenshogaku Zasshi* 1998;**72**:5–11.
19 **Takahashi M**, Nishizawa T, Gotanda Y, *et al*. High prevalence of antibodies to hepatitis A and E viruses and viremia of hepatitis B, C and D viruses among apparently healthy populations in Mongolia. *Clin Diagn Lab Immunol* 2004;**11**:392–8.
20 **Davaalkham D**, Ojima T, Nymadawa P, *et al*. Seroepidemiology of Hepatitis B virus infection in Mongolian children: a nationwide survey. *Pediatr Int*. In press.
21 **Davaalkham D**, Ojima T, Nymadawa P, *et al*. Prevalence and risk factors for hepatitis C virus infection in Mongolian children: findings from a nationwide survey. *J Med Virol* 2006;**78**:466–72.
22 **Hsu HY**, Chang MH, Liaw SH, *et al*. Changes of hepatitis B surface antigen variants in carrier children before and after universal vaccination in Taiwan. *Hepatology* 1999;**30**:1312–17.
23 **Davaalkham D**, Ojima T, Uehara R, *et al*. Analysis of hepatitis B surface antigen mutations in Mongolia: molecular epidemiology and implications for mass vaccination. *Arch Virol* 2007;**152**:575–84.
24 **Davaalkham D**, Ojima T, Uehara R, *et al*. Impact of the universal hepatitis B immunization program in Mongolia: achievements and challenges. *J Epidemiol*. In press.
25 **Lok AS**. Chronic hepatitis B. *N Engl J Med* 2002;**346**:1682–3.
26 **Asian development bank**. Mongolia National Immunization Program financing assessment: Asian vaccination initiative financing assessment. http://www.adb.org/Publications/year.asp (accessed 20 Feb 2007).
27 **Bell KN**, Hogue CJ, Manning C, *et al*. Risk factors for improper vaccine storage and handling in private provider offices. *Pediatrics* 2001;**107**:E100.
28 **Thakker Y**, Woods S. Storage of vaccines in the community: weak link in the cold chain? *BMJ* 1992;**304**:756–8.
29 **Otto BF**, Suarnawa IM, Stewart T, *et al*. At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain. *Vaccine* 1999;**18**:498–502.
30 **Hipgrave DB**, Tran TN, Huong VM, *et al*. Immunogenicity of a locally produced hepatitis B vaccine with the birth dose stored outside the cold chain in rural Vietnam. *Am J Trop Med Hyg* 2006;**74**:255–60.
31 **Hipgrave DB**, Maynard JE, Biggs BA. Improving birth dose coverage of hepatitis B vaccine. *Bull World Health Organ* 2006;**84**:65–71.
32 **National Center for Health Development, Ministry of Health of Mongolia**. *Annual Health Report-2004*, Ulaanbaatar, 2004.http://www.moh.mn/ (accessed 20 Feb 2007).

APHORISM OF THE MONTH

We have not considered the potential of humour in reconciling issues in negotiation and mediation, in reducing inevitable tensions where cultural, social and political differences intersect. Humour is a lubricant that can help get us through the rough patches.

Lowell Levin and JRA